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ORIGINAL REPORT

Multiple Myeloma Treatment Transformed: A Population-Based Study of Changes in Initial Management Approaches in the United States

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ABSTRACT

Purpose
Despite improved outcomes for multiple myeloma, little is known about changes in initial treatment at the population level for US patients. We report trends in treatment practices.

Patients and Methods
Patients (n = 1,976) with newly diagnosed myeloma in 1999, 2003, and 2007 were examined by using the National Cancer Institute's Patterns of Care Studies. We assessed use of common chemotherapies (melphalan, vincristine, and doxorubicin), novel agents (thalidomide, bortezomib, or lenalidomide), or hematopoietic stem-cell transplantation (HSCT) during the first year after diagnosis. By using logistic regression, we evaluated the association of race and insurance status with receipt of high-cost treatments—transplantation or novel agents.

Results
From 1999 to 2007, use of melphalan alone dropped from 32.0% to 4.1%, and vincristine and doxorubicin use declined from 18.2% to 0.4%. The percentage of patients receiving any novel agent rose from 3.9% in 1999 to 75.5% in 2007. HSCT increased from 11.1% in 1999 to 21.7% in 2007. For white patients, use of novel agents was lower for those with Medicare only (42.6%) than for those with private insurance (50.2%). For patients of other races, those with Medicare only or Medicaid were less likely to receive novel agents or transplantation compared with those with private insurance.

Conclusion
Initial treatment for multiple myeloma has changed markedly. Most patients now receive novel agents, with a decline in the use of traditional chemotherapy. Use of transplantation and novel agents varies with race and insurance. These findings document rapid changes in patterns of care and highlight addressable disparities in myeloma care.

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INTRODUCTION

In 2011, approximately 20,500 individuals in the United States were newly diagnosed with multiple myeloma,[1] and approximately 10,600 people died from multiple myeloma and its complications, accounting for approximately 20% of deaths from hematologic malignancies.[2] The median age at diagnosis is 70 years.[3] The number of patients affected by multiple myeloma, a cancer that primarily affects the elderly, is expected to grow over time because of the increasing life expectancy of the population in the United States.

Historically the overall median survival in myeloma has been 19 months.[4] However the 5-year relative survival for multiple myeloma has improved from 28.8% for patients diagnosed from 1990 to 1992 to 34.7% for patients diagnosed from 2002 to 2004.[5] The increased survival likely reflects changes in treatment. In the 1980s, a combination of melphalan and prednisone was considered the standard treatment for multiple myeloma; by the 1990s, the combination of vincristine, doxorubicin, and dexamethasone (VAD) had become generally accepted for refractory disease. Autologous hematopoietic stem-cell transplantation (HSCT) was introduced in the mid-1980s, and by the mid-1990s, it was considered a standard of care for younger patients with adequate renal function.[6,7]

Over the past decade, treatment for multiple myeloma has evolved to include immunomodulatory drugs such as thalidomide and lenalidomide and the targeted proteasome inhibitor bortezomib. These novel agents are being used before and after autologous HSCT, although it is not yet established whether newer agents can be used in place

of transplantation in patients for whom such treatment is generally accepted.[6] The extent to which novel therapies have replaced conventional chemotherapy is also not known.

Although new treatments have increased survival, they have also affected the cost of myeloma treatment. Autologous HSCT has been estimated to cost from $20,000 to 60,000. In 2008, the estimated total treatment cost was $46,588 per patient receiving thalidomide/dexamethasone, $47,792 for those receiving bortezomib/dexamethasone, and $71,672 for patients receiving lenalidomide/dexamethasone.[8] Annual out-of-pocket expenses from 2005 to 2007 were estimated to be $4,443 for thalidomide, $3,504 for bortezomib, and $4,766 for lenalidomide.[9] These high costs may pose access issues for patients who are uninsured or underinsured.

In this article, we report the trends in treatment patterns for US patients with newly diagnosed multiple myeloma for selected years 1999 to 2007. We evaluate the treatments within the first 12 months, including specific chemotherapies, novel agents (thalidomide, lenalidomide, bortezomib), and HSCT. We also examine the association of race and insurance status on the receipt of costly treatments—HSCT and novel agents.

PATIENTS AND METHODS

Data Used and Study Sample

The National Cancer Institute's (NCI's) Surveillance, Epidemiology, and End Results (SEER) cancer registries collect information on all incident cancers occurring in defined geographic regions. The SEER areas, currently covering 28% of the US population,[10] are comparable to the general US population with regard to levels of poverty and education. The SEER population tends to be more urban than the total US population. The SEER registries collect data on date of diagnosis, tumor characteristics, treatment, and selected demographic characteristics. Information for each patient comes primarily from hospitals records. Adjuvant therapy is under-reported in the SEER data because systemic therapies are often provided in the outpatient setting. To obtain information on therapy that is not well-collected by routine SEER activities, NCI annually conducts Patterns of Care (POC) studies on selected cancer sites, collecting information from physicians about their patients' treatment for cancer. Each SEER registry obtains institutional review board approval before initiating the study.

This study included a sample of SEER patients diagnosed with multiple myeloma (International Classification of Diseases, Oncology, 3rd revision [ICD-O-3] Site code: C42 and histology codes M-9731 to M-9732) in 1999, 2003 and 2007. Patients with a previous diagnosis of cancer, a simultaneous second cancer diagnosis, myeloma found on autopsy or on the death certificate, or who were under age 20 were ineligible for the study. Eligible patients were stratified by registry, sex, and racial/ethnic group and were randomly sampled within strata. Sampling weights varied on the basis of the sex and race/ethnicity of the patient. Sampling fractions were used to calculate weighted percentages that reflect SEER populations from which the data were obtained. Women, non-Hispanic blacks, Hispanics, Asian/Pacific Islanders, American Indians, and Alaskan natives were oversampled to obtain more stable estimates.

The total study sample initially consisted of 711 patients diagnosed in 1999, 974 in 2003, and 994 in 2007. The focus of the analysis was on trends associated with initial treatment, defined as treatments in the first 12 months following diagnosis. Each patient was required to survive the entire 12 months, which reduced our final sample for each year of the study by approximately 25%, to 524, 710, and 742 patients, respectively. Because the SEER registries collect the month of cancer diagnosis, but not the exact diagnosis day, we assumed that all patients were diagnosed on the first day of the month.

Abstractors responsible for the POC study from the 14 participating SEER registries (the metropolitan areas of San Francisco/Oakland, Detroit, Seattle, Atlanta, San Jose/Monterey, Los Angeles County, and the states of Connecticut, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah, and the remainder of California) underwent centralized training. Hospital records were abstracted for the sampled patients to verify myeloma characteristics and demographic information. Each patient's physician was asked to indicate all treatments with chemotherapy, novel agents, or HSCT. For quality control, 5% of patients had their records re-abstracted.

Measures and Statistical Analyses

The POC abstraction tool included an extensive list of drugs used to treat multiple myeloma. Although the POC data included several agents, we reported data only on chemotherapies that were most commonly provided in the POC data—melphalan, vincristine, and doxorubicin. Novel agents included thalidomide (1999, 2003, and 2007), bortezomib (2003 and 2007 only), and lenalidomide (2007 only), reflecting the years after US Food and Drug Administration approval for treatment of myeloma. We did not report steroid use because of concerns about underascertainment from the medical record. Information about HSCT included whether or not the procedure was performed.

We calculated the number and percentage of patients who received one agent alone or in specific combinations of the three chemotherapies and the three novel agents that were the focus of our analysis. A patient receiving an agent alone was defined as not receiving any of the other six drugs included in the analysis. We reported combinations of these six drugs in which the prevalence of patients receiving the combined agents was 2.0% or greater in at least one of the three years of data. We also provided information regarding the combined groups of treatments—chemotherapy (all agents combined), novel agents (all agents combined), or HSCT—by examining mutually exclusive combinations of each therapeutic group or those who received no treatment. We used logistic regression models to evaluate the association of age, insurance status, and year of diagnosis with receipt of costly treatments—HSCT or novel agent (thalidomide, bortezomib, or lenalidomide). Insurance was classified into three mutually exclusive groups: patients who had any type of private insurance, patients with Medicare only (no supplemental coverage), or patients with any type of Medicaid. The rationale for grouping insurance in this way is that persons with Medicare only or Medicaid may encounter challenges to access or high copayments that are not faced by persons with private insurance. Persons with unknown insurance or no insurance were excluded from the logistic regression models ($< 6\%$ of patients). Separate models included binary dependent variables: receipt of HSCT and receipt of a novel agent during the 12 months following diagnosis. To increase power, all years of data were combined for the logistic regression analyses. The results of the logistic regression analyses were presented as standardized percentages (predictive margins), representing the average percentage of patients receiving transplantation or novel therapy.[11] The standardized percentages and SEs were adjusted for age group, type of insurance, and year of diagnosis. A prior study reported that the association of insurance status with treatment varied by race.[12] Therefore, the models were stratified by race: one model included non-Hispanic white patients and the other model included patients of other races. We used SUDAAN statistical software (Research Triangle Institute, Research Triangle Park, NC) to account for the sampling design in all analyses. Variances were computed by using the Taylor series linearization method. The fit of the models was assessed by using the Hosmer-Lemeshow test in SUDAAN. All of the models were a good fit to the data.

RESULTS

More than 37% of the patients were age 70 or older (Table 1), and non-Hispanic whites accounted for 65.7% of patients. For all years, 72.1% of the patients had private health insurance, 12.9% of the patients had Medicare only, and 9.3% had Medicaid coverage.

There was a marked change in patterns of use of chemotherapy or novel agents between 1999 and 2007 (Table 2). The percentage of patients who received only melphalan dropped from 32.0% in 1999 to

Table 1. Characteristics of Newly Diagnosed Patients With Multiple Myeloma in the Patterns of Care Data by Year of Diagnosis

Characteristic	1999 (n = 524)		2003 (n = 710)		2007 (n = 742)		Total (N = 1,976)	
	No.	Column Weighted %	No.	Column Weighted %	No.	Column Weighted %	No.	Column Weighted %
Age at diagnosis, years								
< 50	71	13.6	104	12.3	79	9.3	254	11.2
50-59	112	19.9	172	28	160	24.1	444	24.8
60-69	141	27.4	190	24.9	217	28.3	548	26.9
70+	200	39.1	244	34.7	286	38.3	730	37.1
Sex								
Male	278	55.5	356	52.7	381	59.5	1,015	56.2
Female	246	44.5	354	47.3	361	40.5	961	43.8
Race/ethnicity								
Non-Hispanic white	295	68.1	268	63.4	325	66.6	888	65.7
Non-Hispanic black	146	19.7	214	17.9	204	16.4	564	17.5
Hispanic	83	12.2	139	12.3	121	11.3	343	11.8
Asian	—	—	89	6.4	92	5.7	181	4.9
Insurance status								
Private insurance	367	71.5	471	71.4	496	72.9	1,334	72.1
Medicare only	72	14.6	99	12.6	111	12.5	282	12.9
Any Medicaid	43	6.9	93	8.7	101	10.7	237	9.3
No insurance	13	2.4	25	2.3	21	2.0	59	2.2
Unknown	29	4.7	22	4.9	13	1.9	64	3.5

NOTE. All patients were required to survive 12 months after diagnosis.

4.1% in 2007. Use of vincristine and doxorubicin also dropped from 18.2% in 1999 to 0.4% in 2007. The decline in chemotherapy use was offset by increased use of novel agents. Use of thalidomide alone rose from 0.2% in 1999 to 14.4% in 2007. In 2007, the percentage of patients who received bortezomib alone was 7.4% or lenalidomide alone was 7.3%.

Table 3 summarizes the combinations of treatments that US patients with myeloma received. The percentage of patients who received no treatment varied from 29.1% in 1999 to 33.6% in 2003 and 18.7% in 2007. The use of chemotherapy as the only treatment within the year following diagnosis declined from 56.6% in 1999 to 5.0% in 2007; the percentage of patients having any chemotherapy decreased

Table 2. Types of Therapy and Combinations Received Within 12 Months of a New Diagnosis of Multiple Myeloma

Type of Therapy*	1999		2003		2007	
	No.	Column Weighted %	No.	Column Weighted %	No.	Column Weighted %
Melphalan alone†	165	32.0	89	12.2	34	4.1
Thalidomide alone†	1	0.2	98	14.0	100	14.4
Bortezomib alone†			1	0.1	53	7.4
Lenalidomide alone†					69	7.3
Vincristine and doxorubicin	96	18.2	97	11.2	5	0.4
Vincristine and melphalan	14	2.5	9	1.2	1	0.0
Melphalan and thalidomide	6	1.3	53	7.7	59	11.3
Melphalan and bortezomib			1	0.1	17	1.7
Bortezomib and thalidomide			2	0.2	33	5.1
Melphalan and lenalidomide					19	2.8
Bortezomib and lenalidomide					38	5.0
Melphalan, thalidomide, and bortezomib			1	0.1	16	1.6
Thalidomide, lenalidomide, and bortezomib					18	3.0
Melphalan, lenalidomide, and bortezomib					16	3.3
Vincristine, doxorubicin, and thalidomide	7	1.5	30	3.8	5	0.6
Vincristine, melphalan, and doxorubicin	44	7.9	39	5.4	1	0.3
Vincristine, melphalan, doxorubicin, and thalidomide	3	1.0	17	4.8	2	0.2

NOTE. All patients were required to survive 12 months after diagnosis. Columns do not sum to 100 because patients receiving other chemotherapies were not reported.

*Categories limited to use of six drugs: melphalan, vincristine, doxorubicin, thalidomide, bortezomib, and lenalidomide. Use of corticosteroids not shown due to under-reporting.

†Alone defined as not receiving any of the other six drugs assessed in the analysis.

Table 3. Percentage of Patients Being Treated With Chemotherapy, Novel Agents, and Transplantation Within 12 Months of a Multiple Myeloma Diagnosis

Treatment*	1999		2003		2007	
	No.	Column Weighted %	No.	Column Weighted %	No.	Column Weighted %
No treatment†	158	29.1	230	33.6	163	18.7
Chemotherapy only	297	56.6	193	23.2	42	5.0
Novel agents only	1	0.2	91	13.2	301	40.1
Chemotherapy and transplantation	52	10.5	67	10.7	4	0.8
Novel agent and transplantation	0	0.0	10	1.0	24	3.3
Novel agent and chemotherapy	14	3.1	73	10.2	108	14.5
Chemotherapy, novel agents, and transplantation	2	0.6	46	7.9	100	17.6

NOTE. Chemotherapy includes all agents given.
*Groups are mutually exclusive.
†Patients may have received corticosteroids. Use of corticosteroids not shown due to under-reporting.

from 69.3% in 1999 to 37.2% in 2007. The declining use of chemotherapy was offset by the use of novel agents. By 2007, novel agents represented the only therapy provided to 40.1% of patients. The percentage of patients receiving any novel agent rose from 3.9% in 1999 to 75.5% in 2007. Use of HSCT within 12 months of diagnosis increased from 11.1% in 1999 to 21.7% in 2007. There was also a marked change in the percentage of patients treated with the combination of chemotherapy, novel agents, and transplantation.

The association of insurance status and age with receipt of novel agent or transplantation, stratified by race, is presented in Table 4. Among non-Hispanic white patients, the type of insurance was not significantly associated with the receipt of novel agents, although 42.6% of patients with Medicare only received novel agents contrasted with 50.2% of those with private insurance. For patients of other races, use of novel agents was significantly lower among patients with Medicare only (38.0%) or any Medicaid (36.3%) than for patients with private insurance (47.3%) The increased use of novel agents across years was highly significant for both race groups ($P \leq .001$). Insurance status was not associated with receipt of transplantation for non-Hispanic white patients, but for patients of other races, transplantation use was significantly lower among patients with any Medicaid or with Medicare only, even after adjusting for age ($P \leq .001$). For both race groups, the use of transplantation declined significantly with patient age although use of transplantation doubled between 1999 and 2007.

DISCUSSION

We assessed population-based trends in initial treatment among patients with newly diagnosed multiple myeloma in the United States from 1999 to 2007. There were striking changes over this period. In 1999, treatment options were limited primarily to cytotoxic chemotherapy approaches, resulting in a delay in the initiation of therapy during the first year following diagnosis. By 2007, there was increased availability of novel agents. Novel agents have greater efficacy and less treatment-related toxicity,[6] although these drugs have adverse effects such as neuropathy and thrombolytic events. The improved tolerance

Table 4. Standardized Percentages of Patients With Multiple Myeloma Receiving Novel Agents or HSCT in 1999, 2003, and 2007 by Race

Variable	Received Novel Agents						Received Transplantation					
	Non-Hispanic White			Other Races			Non-Hispanic White			Other Races		
	Standardized Percentage*	SE	*P*	Standardized Percentage*	SE	*P*	Standardized Percentage*	SE	*P*	Standardized Percentage*	SE	*P*
Age group, years			< .001			.140			< .001			< .001
< 50	47.6	5.7		42.3	3.9		44.4	6.8		28.1	4.0	
50-59	54.4	4.5		48.9	2.9		33.7	5.2		19.7	2.5	
60-69	52.1	3.4		44.1	2.8		30.1	4.6		11.1	2.0	
70+	44.9	3.2		40.0	2.6		4.0	1.8		1.3	0.8	
Insurance status†			.222			.002			.276			< .001
Private insurance	50.2	2.2		47.3	1.9		22.4	2.3		17.0	1.5	
Medicare only	42.6	4.9		38.0	4.1		28.7	10.2		6.0	1.7	
Any Medicaid	56.0	6.4		36.3	2.7		12.8	5.3		3.9	2.2	
Year of diagnosis			< .001			< .001			.004			.018
1999	5.3	1.4		2.1	1.0		13.7	2.1		7.2	1.8	
2003	33.9	3.9		29.8	2.4		20.3	3.0		14.5	1.7	
2007	78.6	2.7		72.5	2.5		26.6	3.6		15.2	2.0	

Abbreviation: HSCT, hematopoietic stem-cell transplantation.
*Standardized percentages are adjusted by insurance status, age group, and year of diagnosis.
†Patients with no insurance or unknown insurance status were excluded.

to novel agents likely resulted in treatment being introduced earlier in the disease course. By 2007, less than 20% of the patients in our analysis were not treated within 12 months of diagnosis.

From 1999 to 2007, there was a marked decrease in the use of traditional cytotoxic chemotherapeutics for US patients with myeloma. Of particular note, the use of melphalan, which is toxic to the bone marrow and can preclude later stem-cell transplantation, decreased dramatically. This likely reflects the increased availability of novel, efficacious agents and the hope that patients who would not have been candidates for transplantation because of advanced disease may become eligible once they are treated with these agents. During the later years of our study, there were excellent preliminary data supporting the use of a combination of chemotherapy plus novel agents for those ineligible for transplantation (eg, melphalan, prednisone, and thalidomide [MPT][13,14] and bortezomib, melphalan and prednisone [VMP])[15,16] However, we were surprised to find that only 14.5% of patients were receiving chemotherapy and novel agents in 2007. A large number (40.1%) were receiving only novel agents which, during the period of observation, had been shown to be effective only in relapsed or refractory disease.[17,18]

The rate of hematopoietic cell transplantation in the first year after diagnosis doubled from 1999 to 2007 but remained relatively low. The timing of HSCT remains a question. Whether it should be offered as part of initial treatment or at the time of relapse is unclear.[3] Although HSCT has been shown to offer better outcomes than traditional chemotherapy in patients able to undergo the procedure,[19-21] it is still unclear whether the use of novel agents before transplantation or instead of transplantation offers better or equivalent long-term results. In our analysis, we saw only a modest increase in the use of the novel agents with transplantation (3.3% in 2007) or in combination with chemotherapy and transplantation (17.6%) in the first 12 months after diagnosis. These data suggest that deferral of immediate transplantation may be an evolving pattern of care in myeloma therapeutics. Moreover, the increase in up-front transplantation that we found (from 11.1% to 21.7%) may, in fact, reflect clinicians' adoption of the older trial data showing that transplantation may be better than chemotherapy. We may eventually see a decrease in up-front transplantation procedures, too, as treatment with novel agents replaces the up-front transplantation strategy.

The changes that we observed in treatment practices were not seen across all patients groups. Insurance status played a significant role in receipt of novel agents or transplantation, primarily for patients of races other than non-Hispanic white. A prior study of adult patients of all ages reported findings consistent with ours—that nonwhite patients with Medicare only or Medicaid were significantly less likely to receive guideline cancer care than those with private insurance. They found that for white patients, those with any Medicaid or Medicare only were also less likely to receive guideline care.[12] This prior study in combination with our findings demonstrates that there is a complex dynamic between insurance, race, and the receipt of treatment. Health insurance is designed to reduce the financial burden of care. However, Medicare patients without supplemental insurance face a 20% out-of-pocket payment for myeloma medications, which may explain the lower use of costly novel agents among patients with Medicare only in both race groups in our analysis. In addition to financial barriers, elderly patients with myeloma may face challenges in finding an oncologist. A 2008 survey of physicians reported that among medical specialists, 13.7% were not accepting new Medicare patients and 28.2% were not accepting new Medicaid patients.[22]

In our analysis, patients of other races were less likely to receive novel agents or transplantation than were non-Hispanic white patients. The role of race in treatment of blood cancer has been reported in other studies; one reported that access to HSCT for blood cancers varies by race and sex, with women and blacks less likely to receive the procedure.[23] Another study, using the SEER data, found that from 1973 to 2005, black patients with myeloma had overall better survival than white patients; however, there was significant survival improvement among whites over time, with smaller, nonsignificant changes among blacks.[24] The authors concluded that the changes in survival were possibly due to unequal access to novel therapies among blacks. We believe that more research is needed for a more in-depth understanding of the role that insurance and race play in the receipt of treatment for patients with myeloma.

Our study has several limitations. The POC abstractors relied on information from the treating physician. Some treatment information may not have been reported. We could not determine the sequence of treatments occurring in the first year. In addition, patients who died within the first year after diagnosis, potentially the sickest, were excluded because we did not feel we could completely assess their patterns of care. Sixty-three percent of patients who died within 12 months following diagnosis were age 70 or older compared with 37.1% of patient who lived 12 months. Thus, our results likely reflect treatments for patients who had a lower level of clinical severity. However, this issue covers all three assessment periods, so our analysis of changes in treatment patterns over time remains robust. Although we controlled for age and insurance status in our logistic regression models, there may be unmeasured factors that influenced treatment selection. We do not have data on patient experiences or preferences. In addition, these findings reflect practice only in the United States. Use of novel agents may differ in other countries, especially those with national health programs that may limit when novel agents can be used. Finally, our data do not allow us to speculate on treatments after 1 year, an area of increasing importance, given the success of the novel agents in improving progression-free survival and overall survival.[25]

In summary, we found that in less than 10 years, initial myeloma treatment has moved from mostly traditional chemotherapy to novel therapies and that the proportion of patients undergoing HSCT has doubled. This represents a paradigm shift in myeloma treatment. Concomitantly there has been a marked improvement in myeloma survival associated with the use of novel therapies.[5,26] In addition, we found differences in approaches to treatment on the basis of race and insurance status. Both of these features pose challenges that need to be addressed so that more individuals can benefit from the remarkable recent advances in myeloma therapy. Although more research is clearly needed to understand the relationship between the novel agents and transplantation, our data suggest that traditional chemotherapy is being quickly eliminated as initial treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: Joan L. Warren, Linda C. Harlan, Jennifer Stevens, Richard F. Little, Gregory A. Abel
Manuscript writing: All authors
Final approval of manuscript: All authors

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